

SUPPLEMENTAL MATERIAL

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References

Figure S1a. Articles selection diagram for the statements in articles.

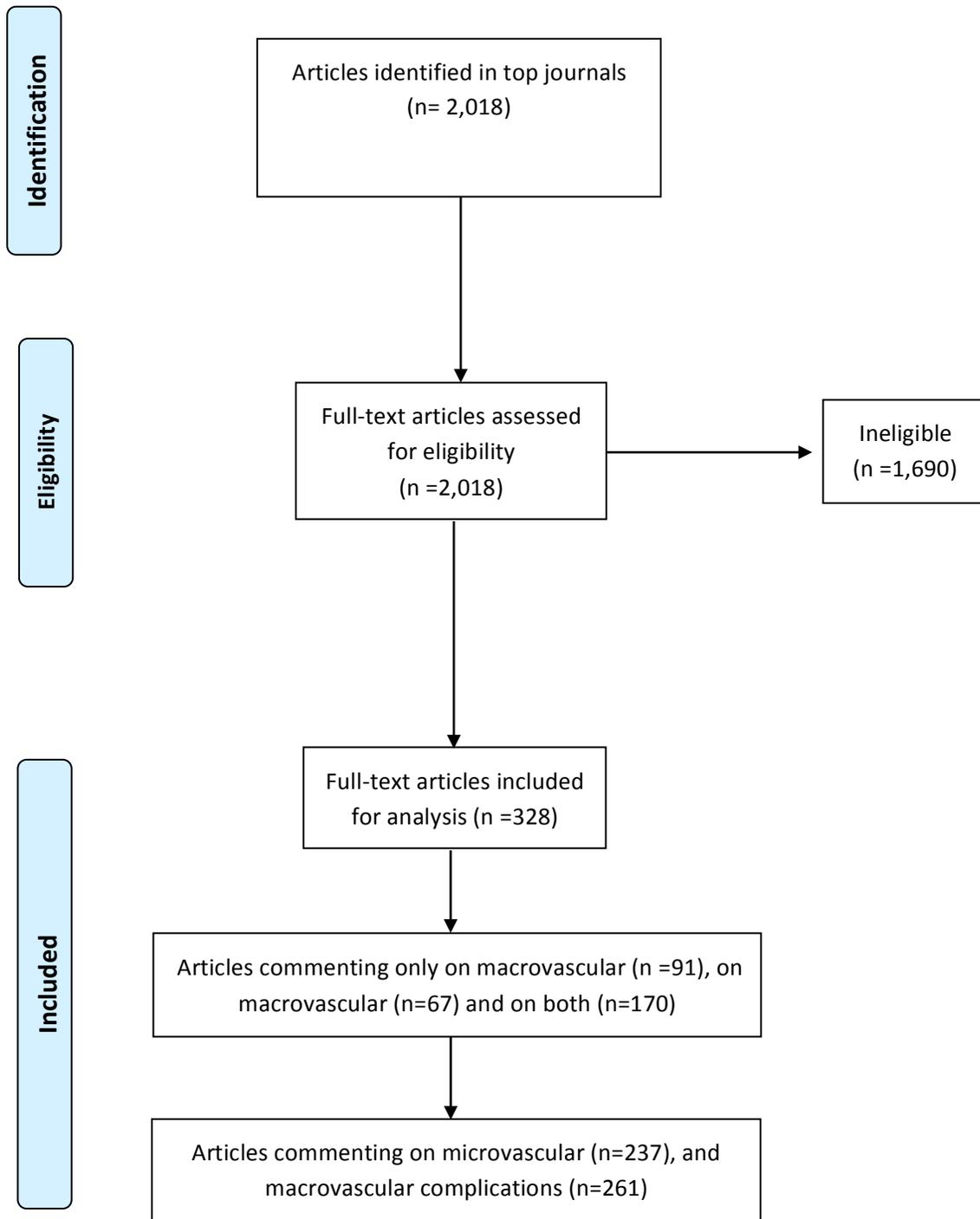
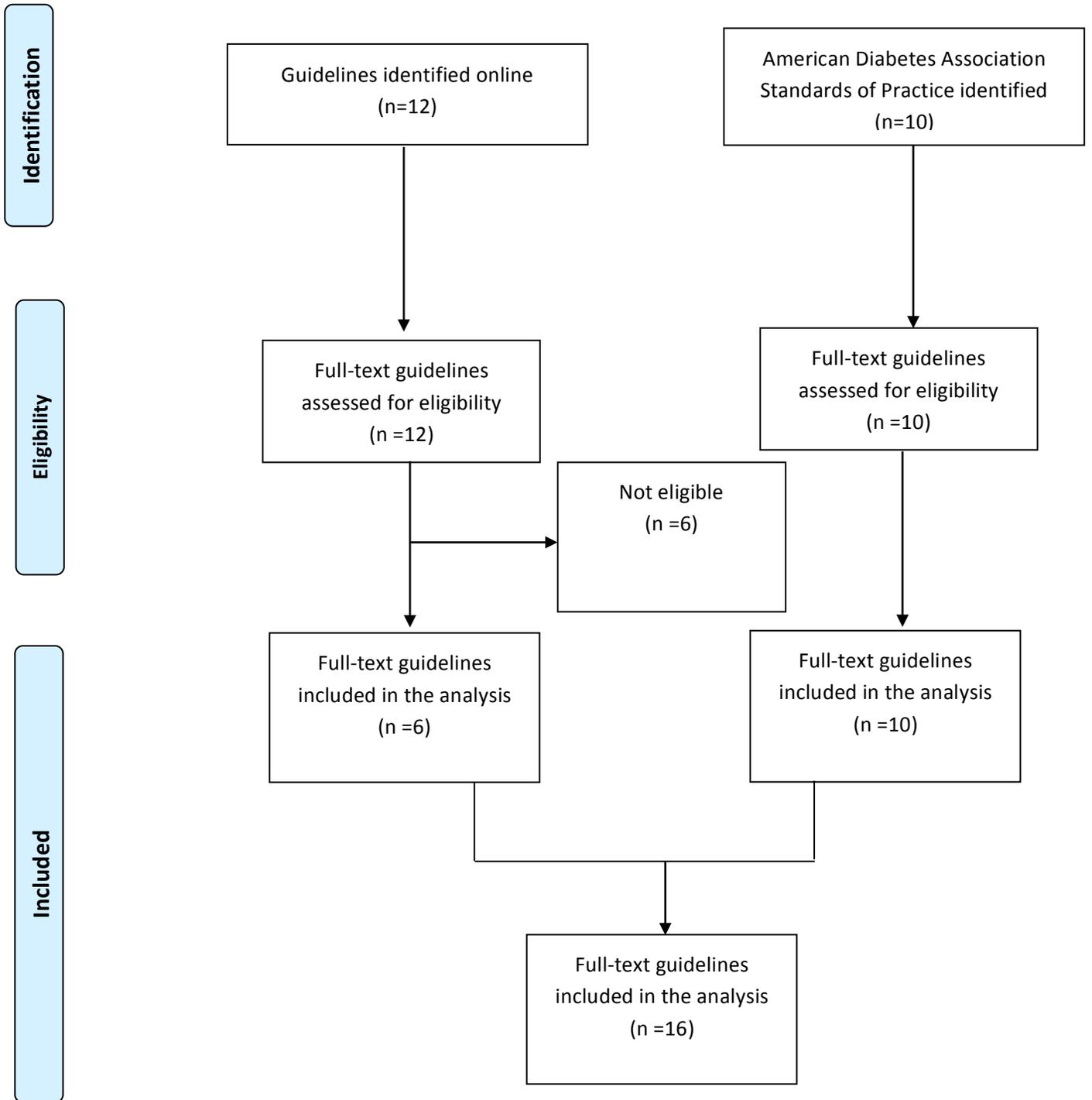


Figure S1b. Clinical practice diabetes guidelines selection diagram.



Not eligible guidelines (due to lack of clear statements with regard micro- or macrovascular diabetes outcomes were the National Institute of Health Excellence, The Japan Diabetes Society, Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), Association Latino Americana de Diabetes (ALAD), Australian Diabetes Society, Joslin Diabetes Center Guidelines

Figure S2. Body of evidence on the effect of glycemic control on severe hypoglycemia.

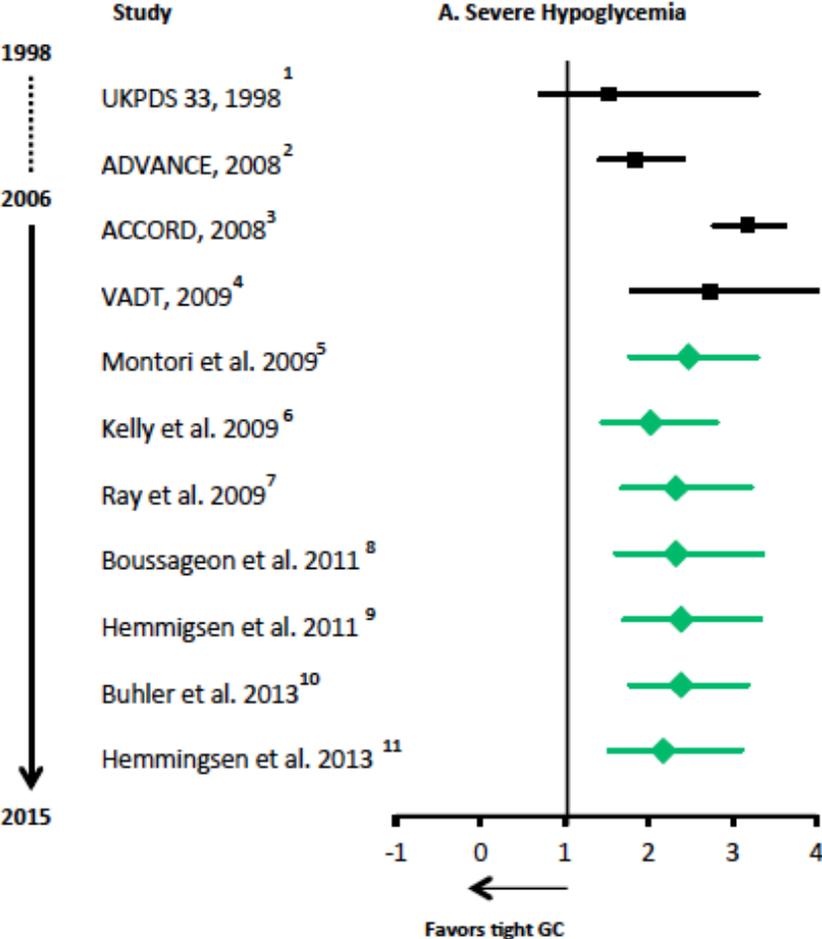
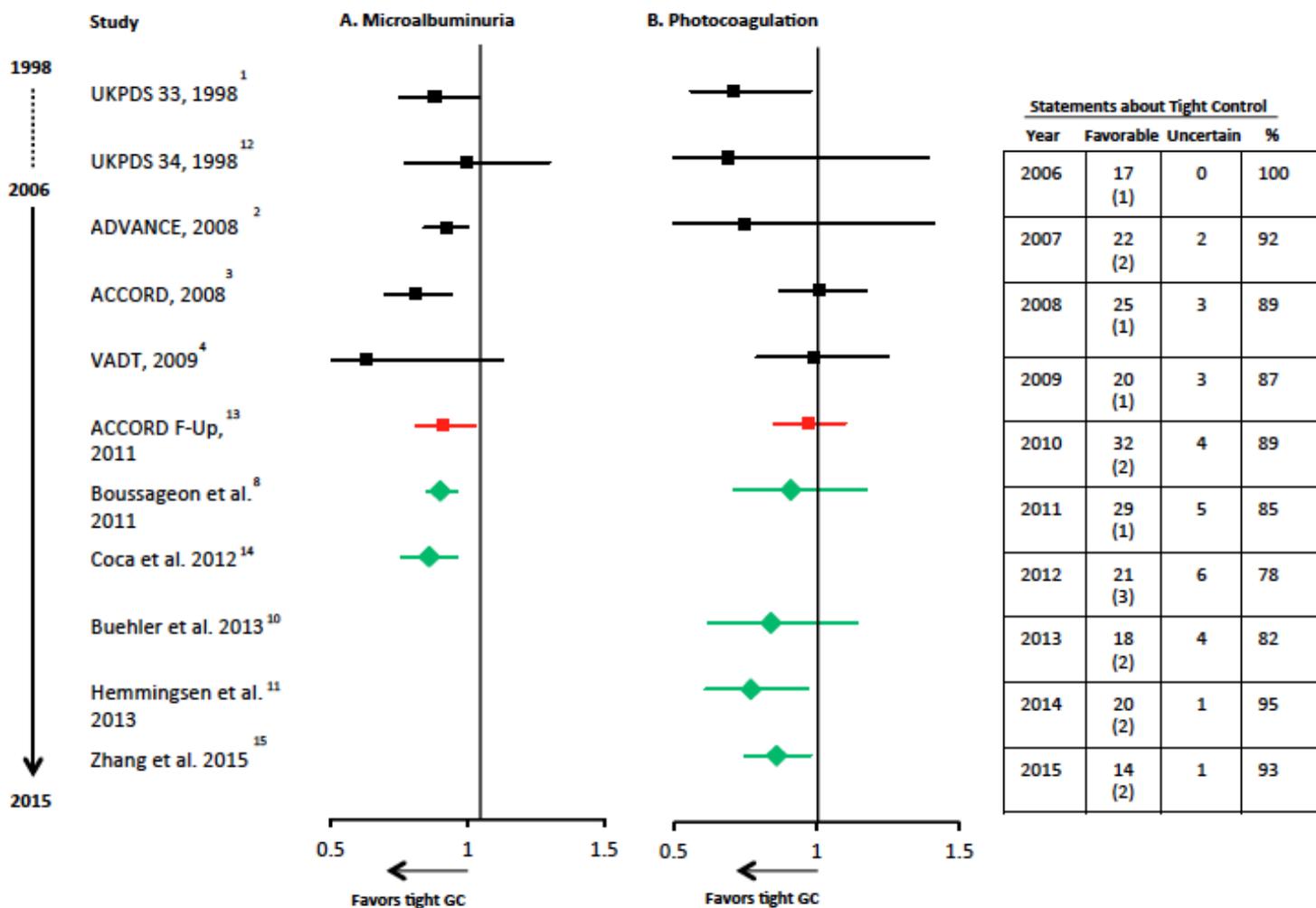


Figure S3. Body of evidence and statements in articles and guidelines in favour of tight glycemic control with regard to microalbuminuria and photocoagulation (surrogate markers)



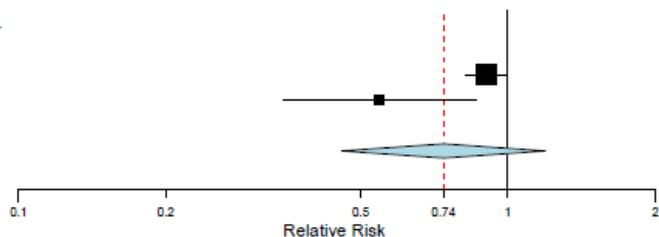
F-Up, follow up; GC, glycemic control; F, Favor; NF, not in favor. In parenthesis the number (n=) of guidelines.

Figure S4. Meta-analysis of extension studies. Including UKPDS 33¹

A. ESRD study

Study names	Weights
ACCORD-FUp ¹³ :	60.7%
ADVANCE-ON FUp ¹⁶ :	39.2%

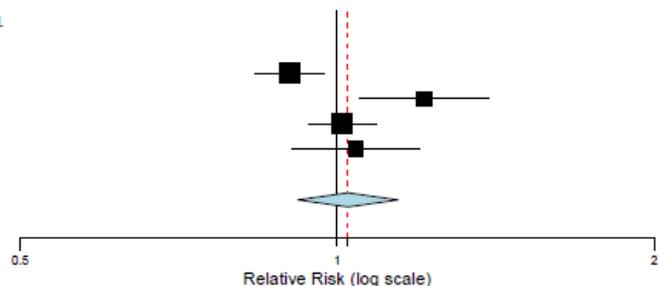
Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
ACCORD-FUp 2011	0.901 (0.820, 0.991)	696/4915	775/4933
ADVANCE-ON FUp 2014	0.547 (0.348, 0.859)	29/5571	53/5569
Overall (I ² =77.83 %, P=0.034)	0.739 (0.457, 1.193)	725/10486	828/10502



B. All-Cause Mortality

Study names	Weights
UKPDS-FUp 33 ¹⁷ :	28.4%
ACCORD-FUp ¹³ :	21.3%
ADVANCE-ON F-Up ¹⁶ :	28.6%
VADT-FUp ¹⁸ :	21.4%

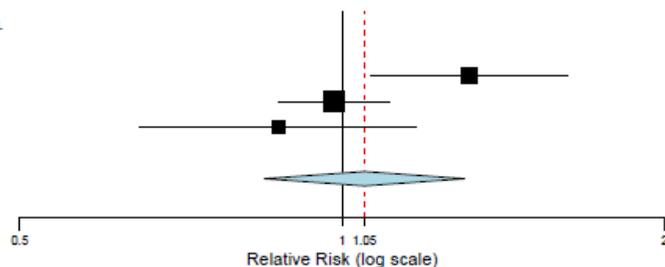
Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
UKPDS-FUp 33 2008	0.902 (0.837, 0.973)	1162/2729	537/1138
ACCORD-FUp 2011	1.210 (1.051, 1.393)	391/4429	327/4483
ADVANCE-ON FUp 2014	1.011 (0.940, 1.088)	1139/5571	1126/5569
VADT-FUp 2015	1.042 (0.906, 1.198)	275/837	258/818
Overall (I ² =79.25 %, P=0.002)	1.024 (0.917, 1.143)	2967/13566	2248/12008



C. CV Mortality†

Study names	Weights
ACCORD-FUp ¹³ :	33.5%
ADVANCE-ON FUp ¹⁶ :	42.1%
VADT-FUp ¹⁸ :	24.3%

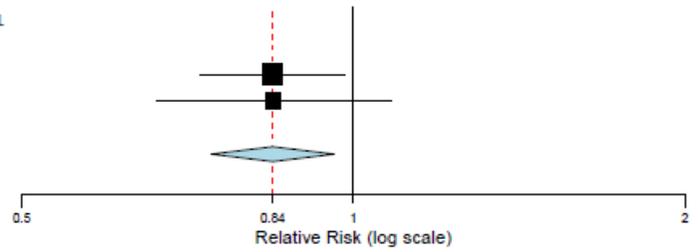
Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
ACCORD-FUp 2011	1.314 (1.062, 1.627)	187/4429	144/4483
ADVANCE-ON FUp 2014	0.984 (0.873, 1.108)	490/5571	498/5569
VADT-FUp 2015	0.871 (0.647, 1.174)	74/837	83/818
Overall (I ² =70.61 %, P=0.033)	1.049 (0.846, 1.302)	751/10837	725/10870



D. Non-Fatal Myocardial Infarctions†

Study names	Weights
ACCORD-FUp ¹³ :	75.254%
VADT-FUp ¹⁸ :	24.746%

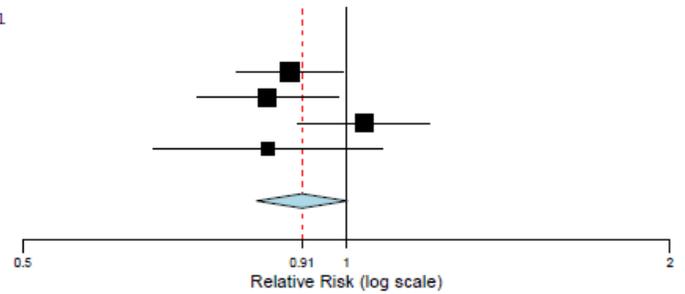
Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
ACCORD-FUp 2011	0.844 (0.726, 0.982)	287/4429	344/4483
VADT-FUp 2015	0.846 (0.662, 1.081)	103/837	119/818
Overall (I ² =0 %, P=0.991)	0.845 (0.743, 0.961)	390/5266	463/5301



E. Fatal and Non-Fatal Stroke[^]

Study names	Weights
UKPDS-FUp 33 ¹⁷ :	19.2%
ACCORD-FUp ¹³ :	12.7%
ADVANCE-ON FUp ¹⁶ :	58.9%
VADT-FUp ¹⁸ :	9.0%

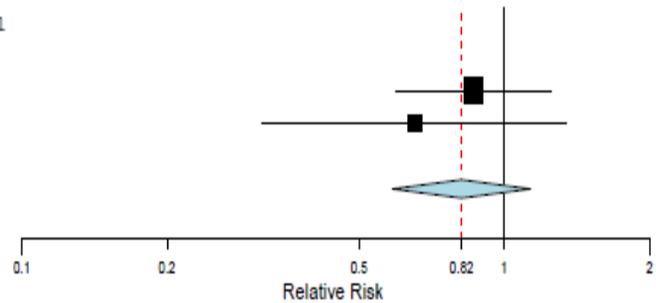
Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
UKPDS-FUp 33 2008	0.886 (0.791, 0.993)	678/2729	319/1138
ACCORD-FUp 2011	0.844 (0.726, 0.982)	287/4429	344/4483
ADVANCE-ON 2014	1.039 (0.902, 1.197)	368/5571	354/5569
VADT-FUp 2015	0.846 (0.662, 1.081)	103/837	119/818
Overall (I ² =38.6 %, P=0.180)	0.909 (0.825, 1.002)	1436/13566	1136/12008



F. Amputations

Study names	Weights
UKPDS-FUp 33 ¹⁷ :	78.665%
VADT-FUp ¹⁸ :	21.335%

Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
UKPDS-FUp 33 2008	0.865 (0.597, 1.254)	83/2729	40/1138
VADT-FUp 2015	0.652 (0.316, 1.344)	12/837	18/818
Overall (I ² =0 %, P=0.494)	0.816 (0.586, 1.135)	95/3566	58/1956



† Did not include neither UKPDS 33¹ or UKPDS 34¹²

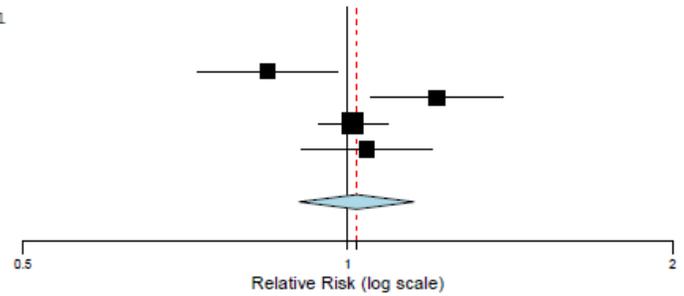
[^] Includes analysis of fatal and non-fatal stroke.

Figure S5. Meta-analysis of extension studies. Including UKPDS 34¹²

A. All-Cause Mortality

Study names	Weights
UKPDS-FUp 34 ⁴¹ :	22.593%
ACCORD-FUp ⁴² :	23.491%
ADVANCE-ON FUp ⁴³ :	30.323%
VADT-FUp ⁴⁴ :	23.593%

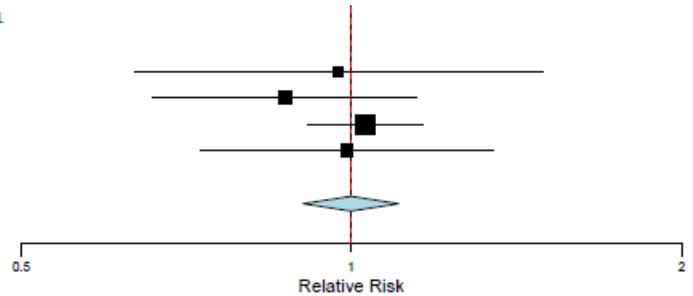
Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
UKPDS-FUp 34 2008	0.842 (0.725, 0.978)	152/342	217/411
ACCORD-FUp 2011	1.210 (1.051, 1.393)	391/4429	327/4483
ADVANCE-ON FUp 2014	1.011 (0.940, 1.088)	1139/5571	1126/5569
VADT-FUp 2015	1.042 (0.906, 1.198)	275/837	258/818
Overall (I²=75.26 %, P=0.007)	1.019 (0.901, 1.152)	1957/11179	1928/11281



B. Fatal and Non-Fatal Stroke[^]

Study names	Weights
UKPDS-FUp 34 ⁴¹ :	5.2%
ACCORD-FUp ⁴² :	14.9%
ADVANCE-ON FUp ⁴³ :	69.1%
VADT-FUp ⁴⁴ :	10.6%

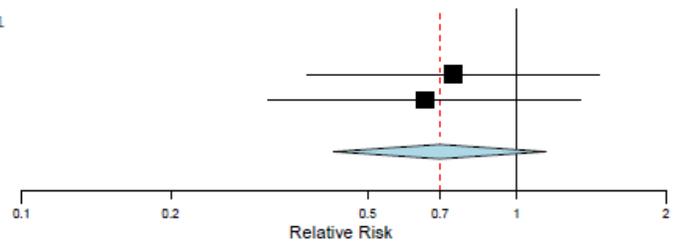
Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
UKPDS-FUp 34 2008	0.973 (0.634, 1.494)	34/342	42/411
ACCORD-FUp 2011	0.869 (0.659, 1.146)	91/4429	106/4483
ADVANCE-ON FUp 2014	1.029 (0.912, 1.161)	491/5571	477/5569
VADT-FUp 2015	0.991 (0.729, 1.346)	75/837	74/818
Overall (I²=0 %, P=0.747)	0.999 (0.903, 1.105)	691/11179	699/11281



C. Amputations

Study names	Weights
UKPDS-FUp 34 ⁴¹ :	52.064%
VADT-FUp ⁴⁴ :	47.936%

Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
UKPDS-FUp 34 2008	0.744 (0.378, 1.464)	13/342	21/411
VADT-FUp 2015	0.652 (0.316, 1.344)	12/837	18/818
Overall (I²=0 %, P=0.793)	0.699 (0.427, 1.147)	25/1179	39/1229



[^] Includes analysis of fatal and non-fatal stroke.

Table S1. Meta-analysis, RCTs and extension studied included as part of the body of evidence.**S1a. Meta-analysis that included only core studies of glycemic control**

Study/ Year Pub.	Included Studies	No. Patients	Outcomes Reported
Montori et al. 2009 ⁵	UKPDS 33 UKPDS 34 ADVANCE ACCORD VADT	28 753	Microvascular Macrovascular Hypoglycemia
Kelly et al. 2009 ⁶	UKPDS 33 UKPDS 34 ADVANCE ACCORD VADT	27 802	Macrovascular Hypoglycemia

S1b. Meta-analysis that included other studies besides 5 Core Studies.

Study/ Year Pub.	Included Studies	No. Patients	Outcomes Reported
Ray et al. 2009 ⁷	UKPDS 33,34 PROactive ADVANCE VADT ACCORD	33 040	Macrovascular Hypoglycemia
Trák I. 2009 ¹⁹	UKPDS PROactive ADVANCE ACCORD VADT	32 629	Macrovascular
Boussageon et al. 2011 ⁸	13 Trials* Including: UGDP (1975,76 and 1982) Kumamoto PROactive HOME	34 533	Microvascular Macrovascular Hypoglycemia
Hemmingsen et al. 2011 ⁹	14 Trials* Including: UGDP REMBO Service et al. Kumamoto VA CSDM	28 614	Microvascular Macrovascular Hypoglycemia
Coca et al. 2012 ¹⁴	Kumamoto UKPDS 33 UKPDS 34 VADT ACCORD ADVANCE VA CSDM	28 065	Microvascular (Renal Endpoints)
Callaghan et al. 2012 ²⁰	ACCORD Azad et al. VADT Tovi et al.	6669	Microvascular (Neuropathy)
Buehler et al. 2013 ¹⁰	Kumamoto UKPDS ADVANCE ACCORD VADT VA CSDM	27 654	Microvascular Macrovascular Hypoglycemia
Hemmingsen et al. 2013 ¹¹	28 Trials* Including: UGDP (1975)	34 912	Microvascular Macrovascular Hypoglycemic

	Kumamoto Steno-2 Service et al. ADDITION- Europe, Leicester, Netherlands REMBO IDA DIGAMI 2 VA CSDM		
Zhang et al. 2015 ¹⁵	Kumamoto UKPDS 33 UKPDS 34 ADVANCE ACCORD VADT VA CSDM AdRem	32 523	Microvascular (Retinopathy)

*Also included in their analysis UKPDS, ACCORD, ADVANCE and VADT.

Table S1c. Randomized clinical trials included.

Study/ Year Pub.	Location	Total N=	Mean HbA1c	CVD	Lost F-Up	Duration of Diabetes Dx.	Trial Duration	Glycemic Target Intensive	HbA1c Achieved Intensive	Glycemic Target Con.	HbA1c Achieved Con.
UKPDS 33 1998 ¹	United Kingdom 23 Centers	3867	7.1%	0%	4%	Recent Diagnosis	10.1 years	FPG <108 mg/dl	7.0%	Best Achievable FPG	7.9%
UKPDS 34 1998 ¹²	United Kingdom	753	7.2%	0%	3%	Recent Diagnosis	10.7 Years	FPG <108 mg/dl	7.0%	Best Achievable FPG	8.0%
ACCORD 2008 ³	US and CA 77 Centers	10 251	8.3%	35%	9%	10 years	3.7 Years	HbA1c < 6.0%	6.4%	HbA1c 7.0-7.9%	7.5%
ADVANCE 2008 ²	215 Centers 20 Countries	11 140	7.5%	32%	14%	8 years	5 years	HbA1c < 6.5%	6.5%	HbA1c Per Local Guidelines	7.3%
VADT 2009 ⁴	US 20 Centers	1791	9.4%	40%	4%	11.5	5.6 years	HbA1c < 6.0%	6.9%	HbA1c 8.0-9.0%	8.4%

Table S1d. Extension studies.

Study/ Year Pub.	Total Follow-Up	Post-Trial Follow-Up	No. Initial Patients	No. Patients Follow-Up	HbA1c End of Study Intensive	HbA1c End of Follow-Up Intensive	HbA1c End of Study Conventional	HbA1c End of Follow-Up Conventional
UKPDS 33 2008 ¹⁷	16.8 years	8.5 years	3867	2998	7.0%	7.9%	7.4%	8.5%
UKPDS 34 2008 ¹⁷	17.7 years	8.8 years	1704	588	7.0%	8.4%	8.0%	8.9%
ACCORD 2011 ¹³	5.0 years	1.3 years	10 251	8912	6.4%	7.2%	7.5%	7.6%
ADVANCE 2014 ¹⁶	9.9 years	5.4 years	11 140	5131	6.5%	7.5%	7.3%	7.5%
VADT 2015 ¹⁸	9.8 years	4.2 years	1791	1391	6.9%	7.8%	8.4%	8.3%*

*Exact data only available for 1st year after end of study.

Table S2. Articles included by year and journal.

Journal	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total (%)
NEJM	2	6	7	3	8	1	6	5	3	0	41 (12.5)
The Lancet	1	0	5	11	6	3	4	3	5	2	40 (12.2)
JAMA	2	7	3	5	4	6	2	3	7	1	40 (12.2)
The BMJ	4	2	3	2	5	9	7	6	1	1	40 (12.2)
Annals of IM	0	4	10	9	4	5	9	0	1	2	44 (13.4)
JACC	1	2	1	4	6	1	5	4	0	0	24 (7.3)
Diabetes Care	7	5	10	8	10	18	6	6	13	16	99 (30.2)
Total	17	26	39	42	43	43	39	27	30	22	328

NEJM, New England Journal of Medicine; JAMA, Journal of the American Medical Association; BMJ, British Medical Journal; IM, Internal Medicine; JACC, Journal of the American College of Cardiology

Table S3. American Diabetes Association guidelines 1998-2015 and their position regarding tight glycemc control.

Guideline	Year	Microvascular	Macrovascular	HbA1c Goal
American Diabetes Association ²¹	2006	Favourable	Uncertain	<6.0-7.0%
American Diabetes Association ²²	2007	Favourable	Uncertain	<6.0-7.0%
American Diabetes Association ²³	2008	Favourable	Uncertain	<6.0-7.0%
American Diabetes Association ²⁴	2009	Favourable	Uncertain	<7.0%*
American Diabetes Association ²⁵	2010	Favourable	Uncertain	<7.0%*
American Diabetes Association ²⁶	2011	Favourable	Uncertain	<7.0%*
American Diabetes Association ²⁷	2012	Favourable	Uncertain	<7.0%*
American Diabetes Association ²⁸	2013	Favourable	Uncertain	<7.0%*
American Diabetes Association ²⁹	2014	Favourable	Uncertain	<7.0%*
American Diabetes Association ³⁰	2015	Favourable	Uncertain	<7.0%*

*More or less stringent glycemc goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

Table S4. Latest version of included guidelines and their position regarding tight glycemic control.

Guideline	Year	Microvascular	Macrovascular	HbA1c Goal
Department of Veterans Affairs and The Department of Defense ³¹	2010	Favourable	Uncertain	<7.0%*
American Diabetes Association/European Association for the Study of Diabetes ³²	2012	Favourable	Uncertain	<7.0%*
International Diabetes Federation ³³	2012	Favourable	Uncertain	<7.0%*
Canadian Diabetes Association ³⁴	2013	Favourable	Uncertain	≤ 7.0%*
The Royal Australian College of General Practitioners ³⁵	2014-2015	Favourable	Uncertain	≤ 7.0%*
American Association of Clinical Endocrinologists/ American College of Endocrinology ³⁶	2015	Favourable	Uncertain	≤ 6.5%*

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations

Table S5. Point estimates and 95% confidence intervals for microvascular outcomes.

Study/Year	ESRD or Dialysis	Renal Death	Blindness	Clinical Neuropathy
UKPDS 33 1998 ¹	0.73 (0.25-2.14)	1.63 (0.21-12.49)	0.84 (0.51-1.40)	0.95 (0.76-1.18)
UKPDS 34 1998 ¹²	1.14 (0.09-14.94)	2.44 (0.10-57.46)	1.07 (0.38-2.99)	-
ADVANCE 2008 ²	0.35 (0.15-0.83)	0.85 (0.45-1.62)	1.01 (0.97-1.04)	1.02 (0.97-1.06)
VADT 2009 ⁴	0.64 (0.25-1.64)	-	0.71 (0.35-1.46)	0.99 (0.82-1.20)
Montori et al. 2009 ⁵	0.76 (0.47-1.23) I ² =0%	-	1.00 (0.93-1.07) I ² =0%	0.95 (0.84-1.08) I ² =50%
ACCORD 2010 ³	0.95 (0.73-1.24)	-	0.95 (0.80-1.13)	0.93 (0.87-1.01)
ACCORD F-Up 2011 ¹³	0.92 (0.73-1.16)	-	1.01 (0.88-1.16)	0.92 (0.86-1.01)
Boussageon et al. 2011 ⁸	1.03 (0.98-1.08) I ² =0%	-	1.00 (0.96-1.05) I ² =0%	0.99 (0.95-1.03) I ² =0%
Coca et al. 2012 ¹⁴	0.69 (0.46-1.05) I ² =43%	0.99 (0.55-1.79) I ² =0%	-	-
Callaghan et al. 2012 ²⁰	-	-	-	0.94 (0.90-1.00) I ² =0%
Buehler et al. 2013 ¹⁰	0.74 (0.33—1.64) I ² =NR	-	0.88 (0.60-1.27) I ² =NR	-
Hemmingsen et al. 2013 ¹¹	0.87 (0.71-1.06) I ² =0%	-	-	-
ADVANCE-ON 2014 ¹⁶	0.54 (0.34-0.85)	0.89 (0.60-1.31)	0.97 (0.83-1.13)	-
Zhang et al. 2015 ¹⁵	-	-	0.99 (0.86-1.13) I ² =0%	-
Meta-analysis F-Up Studies 2015	0.73 (0.46-1.16) I ² =77%	-	-	-

NR, not reported. I²= Heterogeneity

Table S6. Point estimates and 95% confidence intervals for macrovascular outcomes.

Study/Year	All-Cause Mortality	CV Mortality	Non-Fatal MI	Stroke	Amputations/ PVD
UKPDS 33 1998 ¹	0.94 (0.80-1.10)	0.91 (0.75-1.12)	0.79 (0.58-1.09)	1.07 (0.68-1.69)*	0.61 (0.28-1.33)
UKPDS 34 1998 ¹²	0.62 (0.42-0.90)	0.57 (0.36-0.89)	0.69 (0.35-1.34)	0.42 (0.12-1.45)*	0.74 (0.19-2.89)
ADVANCE 2008 ²	0.93 (0.83-1.06)	0.94 (0.84-1.06)	0.98 (0.79-1.22)	0.97 (0.81-1.15)	0.94 (0.81-1.08)
ACCORD 2008 ³	1.26 (1.06-1.51)	1.43 (1.11-1.86)	0.79 (0.66-0.95)	1.05 (0.77-1.45)	-
UKPDS F-Up 2008 ¹⁷	0.87 (0.79-0.96)	-	0.85 (0.74-0.97) [§]	0.91 (0.73-1.13)	0.82 (0.56-1.19)
UKPDS F-Up MTF 2008 ¹⁷	0.73 (0.59-0.89)	-	0.67 (0.51-0.89) [§]	0.80 (0.50-1.27)	0.63 (0.32-1.27)
VADT 2009 ⁴	1.08 (0.83-1.41)	1.32 (0.83-2.11)	0.78 (0.55-1.11)	0.78 (0.48-1.27)	0.65 (0.31-1.36)
Montori et al. 2009 ⁵	0.96 (0.78-1.16) I ² =78%	0.97 (0.74-1.26) I ² =76%	0.82 (0.74-0.93) I ² =0%	0.98 (0.86-1.12) I ² =0%	0.89 (0.77-1.04) I ² =0%
Kelly et al. 2009 ⁶	0.98 (0.84-1.15) I ² =72%	0.97 (0.76-1.24) I ² =76%	0.84 (0.75-0.94) I ² =0%	0.98 (0.82-1.17)* I ² =0%	0.91 (0.79-1.03) I ² =0%
Ray et al. 2009 ⁷	1.02 (1.02-1.19) I ² =NR	-	0.83 (0.75-0.93) I ² =NR	0.93 (0.81-1.06) I ² =NR	-
Trák I. 2009 ¹⁹	1.02 (0.89-1.16) I ² <50%	1.03 (0.84-1.26) I ² >50%	0.84 (0.75-0.93) I ² <50%	0.97 (0.85-1.10)* I ² <50%	-
ACCORD F-Up 2011 ¹³	1.19 (1.03-1.38)	1.29 (1.04-1.60)	0.82(0.70-0.96)	0.86 (0.65-1.13)	-
Boussageon et al. 2011 ⁸	1.04 (0.91-1.19) I ² =42%	1.11(0.86-1.43) I ² =61%	0.85 (0.74-0.96) I ² =0%	1.00 (0.83-1.21)* I ² =0%	0.98 (0.84-1.13) I ² =34%
Hemmingsen et al. 2011 ⁹	1.02 (0.91-1.13) I ² =30%	1.11(0.92-1.35) I ² =46%	0.85 (0.76-0.95) I ² =0%	-	-
Buehler et al. 2013 ¹⁰	1.03 (0.90-1.17) I ² =50%	1.04 (0.83-1.29) I ² =60%	0.85 (0.76-0.95) I ² =0%	1.02 (0.88-1.17)* I ² =0%	0.69 (0.44-1.08) I ² =0%
Hemmingsen et al. 2013 ¹¹	1.0 (0.92-1.08) I ² =16%	1.06 (0.94-1.21) I ² =20%	0.87 (0.77-0.98) I ² =13%	1.0 (0.84-1.19)* I ² =21%	0.65 (0.45-0.94) I ² =0%
ADVANCE-ON 2014 ¹⁶	1.00 (0.92-1.08)	0.97 (0.86-1.10)	-	1.01 (0.89-1.15)	-
VADT F-Up 2015 ¹⁸	1.05 (0.89-1.25)	0.88 (0.64-1.20)	0.85 (0.65-1.11)	0.98 (0.71-1.36)*	0.67 (0.32-1.39)
Meta-analysis F-Up Studies (UKPDS 33 ¹) 2015	1.02 (0.91-1.14) I ² =79%	1.05 (0.85-1.30) † I ² =70%	0.85 (0.74-0.96) † I ² =0%	0.99 (0.89-1.08)^ I ² =0%	0.82 (0.59-1.14) I ² =0%
Meta-analysis F-Up Studies (UKPDS 34 ¹²) 2015	1.02 (0.90-1.15) I ² =75%			0.99 (0.90-1.11)^ I ² =0%	0.70 (0.43-1.15) I ² =0%

† Did not include neither UKPDS 33¹ or UKPDS 34¹²

* UKPDS 33¹, UKPDS 34¹², Kelly et al⁶, Trák I.¹⁹, Boussageon et al⁸, Hemmingsen et al.⁹, Buehler et al.¹⁰, and VADT F-Up¹⁸ are only non-Fatal Strokes

§ Includes Fatal and Non-Fatal MI

^ Includes analysis of fatal and non-fatal stroke.

NR, not reported. I²= Heterogeneity

Table S7. Point estimates and 95% confidence intervals for severe hypoglycemia.

Study/Year	Severe Hypoglycemia
UKPDS 33 1998 ¹	1.99 (1.58-2.51)
ADVANCE 2008 ²	1.85 (1.42-2.42)
ACCORD 2008 ³	3.18 (2.78-3.63)
VADT 2009 ⁴	2.74 (1.8-4.17)
Montori et al. 2009 ⁵	2.48 (1.79-3.29) I ² =83%
Kelly et al. 2009 ⁶	2.03 (1.46-2.81) I ² =84%
Ray et al. 2009 ⁷	2.37 (1.72-3.25) I ² =NR
Boussageon et al. 2011 ⁸	2.33 (1.62-3.36) I ² =63%
Hemmingsen et al. 2011 ⁹	2.39 (1.71-3.34) I ² =73%
Buehler et al. 2013 ¹⁰	2.39 (1.79-3.18) I ² =62%
Hemmingsen et al. 2013 ¹¹	2.18 (1.53-3.11) I ² =66%

NR, not reported. I²= Heterogeneity

Table S8. Point estimates and 95% confidence intervals for microalbuminuria and photocoagulation.

Study/Year	Microalbuminuria	Photocoagulation
UKPDS 33 1998 ¹	0.88 (0.75-1.04)	0.71 (0.53-0.98)
UKPDS 34 1998 ¹²	1.00 (0.77-1.30)	0.69 (0.34-1.39)
ADVANCE 2008 ²	0.92 (0.84-1.00)	0.75 (0.39-1.41)
ACCORD 2008 ³	0.81 (0.70-0.94)	1.01 (0.87-1.17)
VADT 2009 ⁴	0.63 (0.35-1.13)	0.99 (0.79-1.25)
ACCORD F-Up 2011 ¹³	0.91 (0.81-1.03)	0.97 (0.85-1.10)
Boussageon et al. 2011 ⁸	0.90 (0.85-0.96) I ² =31%	0.91 (0.71-1.17) I ² =57%
Coca et al. 2012 ¹⁴	0.86 (0.76-0.96) I ² =64%	-
Buehler et al. 2013 ¹⁰	-	0.84 (0.62-1.14) I ² =73%
Hemmingsen et al. 2013 ¹¹	-	0.77 (0.61-0.97) I ² =43%
Zhang et al. 2015 ¹⁵	-	0.86 (0.75-0.98) I ² =12%

NR, not reported. I²= Heterogeneity

Table S9. Risk of Bias Assessment for randomized included studies

Study	Year	Random Sequence Generation	Allocation Concealment	Blinding Participants and Personnel	Blinding outcome assessment	Incomplete data outcome	Were there any imbalances at baseline?	Reporting Bias	Other bias	% of lost to follow up
UKPDS 33 ¹	1998	Yes	Yes	No blinding	Yes	No	No	No	No	Low
UKPDS 34 ¹²	1998	Yes	Yes	No blinding	Yes	No	No	No	No	Low
ACCORD ³	2008	Yes	Yes	No blinding	Yes	No	No	No	No	Low
ADVANCE ²	2008	Yes	Yes	No blinding	Yes	No	No	No	No	Low
VADT ⁴	2009	Yes	Yes	No blinding	YEs	No	No	No	No	Low

Cochrane assessment tool for RCTs

Table S10. Risk of bias assessment for extension studies.

Study	Year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at baseline	Comparability of cohorts on the basis of design or analysis	Assessment of the outcome	Was follow up enough for outcomes to occur?	Adequacy of follow up of cohorts
UKPDS ¹⁷	2008	Somewhat representative	Drawn from the same community as exposed cohort	Secure Record	Yes	Study controls	Yes	Yes	Lost of follow up likely to introduce bias >20%
UKPDS ¹⁷	2008	Somewhat representative	Drawn from the same community as exposed cohort	Secure Record	Yes	Study controls	Yes	Yes	Lost of follow up likely to introduce bias >20%
ACCORD ³	2011	Truly representative	Drawn from the same community as exposed cohort	Secure Record	Yes	Study controls	Yes	Yes	Los of follow up unlikely to introduce bias
ADVANCE ²	2014	Truly representative	Drawn from the same community as exposed cohort	Secure Record	Yes	Study controls	Yes	Yes	Lost of follow up likely to introduce bias >20%
VADT ⁴	2015	Somewhat representative	Drawn from the same community as exposed cohort	Secure Record	Yes	Study controls	Yes	Yes	Lost of follow up likely to introduce bias >20%

Modified Ottawa classification for observational studies

Table S11. Risk of bias assessment for included systematic reviews.**Domain 1:** Study eligibility criteria

Study	Year	Did the review adhere to pre-defined objectives and eligibility criteria?	Were the eligibility criteria appropriate for the review question?	Were eligibility criteria unambiguous?	Were all restrictions in eligibility criteria based on study characteristics appropriate?	Were any restrictions in eligibility criteria based on sources of information appropriate?	Concerns regarding specification of study eligibility criteria
Montori et al. ⁵	2009	Y	Y	PN	Y	PY	Low
Kelly et al. ⁶	2009	Y	Y	PN	Y	PY	Low
Ray et al. ⁷	2009	Y	Y	N	Y	Y	Low
Trák I. ¹⁹	2009	PY	N	PY	PN	PN	High
Boussageon et al. ⁸	2011	Y	Y	N	Y	Y	Low
Hemmingsen et al. ⁹	2011	Y	Y	N	Y	PY	Low
Coca et al. ¹⁴	2012	Y	Y	PN	Y	PY	Low
Callaghan et al. ²⁰	2012	Y	Y	PN	PY	PY	Low
Buehler et al. ¹⁰	2013	PY	PY	PN	PY	PN	Low
Hemmingsen et al. ¹¹	2013	Y	Y	N	Y	Y	Low
Zhang et al. ¹⁵	2015	PY	PY	PN	PN	PN	High

Domain 2: Identification and selection of studies

Study	Year	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Were methods additional to database searching used to identify relevant reports?	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Were restrictions based on date, publication format, or language appropriate?	Were efforts made to minimize error in selection of studies?	Concerns regarding methods used to identify and/or select studies
Montori et al. ⁵	2009	NI	NI	NI	NI	NI	Unclear
Kelly et al. ⁶	2009	PN	PY	Y	PN	PN	Low
Ray et al. ⁷	2009	Y	Y	Y	PN	Y	Low
Trák I. ²¹	2009	PN	N	N	PN	PN	High
Boussageon et al. ⁸	2011	Y	Y	Y	Y	Y	Low
Hemmingsen et al. ⁹	2011	Y	Y	Y	Y	Y	Low
Coca et al. ¹⁴	2012	Y	Y	Y	Y	Y	Low
Callaghan et al. ²⁰	2012	Y	Y	Y	Y	Y	Low
Buehler et al. ¹⁰	2013	Y	PY	PY	PY	PY	Low
Hemmingsen et al. ¹¹	2013	Y	Y	Y	Y	Y	Low
Zhang et al. ¹⁵	2015	PN	PN	PN	PN	PN	High

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Domain 3: Data collection and study appraisal

Study	Year	Were efforts made to minimize error in data collection?	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Were all relevant study results collected for use in the synthesis?	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Were efforts made to minimize error in risk of bias assessment?	Concerns regarding methods used to collect data and appraise studies
Montori et al. ⁵	2009	NI	NI	NI	NI	NI	Unclear
Kelly et al. ⁶	2009	PN	Y	Y	PY	Y	Low
Ray et al. ⁷	2009	PY	Y	Y	PY	PY	Low
Trák I. ¹⁹	2009	PN	N	PN	PN	N	High
Boussageon et al. ⁸	2011	PY	Y	Y	Y	Y	Low
Hemmingsen et al. ⁹	2011	PY	Y	Y	Y	Y	Low
Coca et al. ¹⁴	2012	PY	Y	Y	Y	Y	Low
Callaghan et al. ²⁰	2012	PY	Y	Y	Y	Y	Low
Buehler et al. ¹⁰	2013	PY	PY	PY	Y	Y	Low
Hemmingsen et al. ¹¹	2013	PY	Y	Y	Y	Y	Low
Zhang et al. ¹⁵	2015	PN	PN	PN	Y	PY	High

Domain 4: Synthesis and findings

Study	Year	Did the synthesis include all studies that it should?	Were all pre-defined analyses reported or departures explained?	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Were biases in primary studies minimal or addressed in the synthesis?	Concerns regarding the synthesis and findings
Montori et al. ⁵	2009	PY	PN	PY	PN	PN	PY	Low-Moderate
Kelly et al. ⁶	2009	Y	PY	PY	Y	PY	PY	Low
Ray et al. ⁷	2009	Y	Y	PY	PY	Y	PY	Low
Trák I. ¹⁹	2009	PN	PN	PN	PY	PN	PN	High
Boussageon et al. ⁸	2011	Y	Y	PY	PY	PY	PY	Low
Hemmingsen et al. ⁹	2011	Y	Y	Y	PY	PY	PY	Low
Coca et al. ¹⁴	2012	Y	Y	Y	PY	PY	PY	Low
Callaghan et al. ²⁰	2012	Y	Y	Y	Y	PY	PY	Low
Buehler et al. ¹⁰	2013	Y	Y	PY	PY	PY	PY	Low

Hemmingsen et al. ¹¹	2013	Y	Y	Y	PY	PY	PY	Low
Zhang et al. ¹⁵	2015	PN	PY	PN	PN	PY	PY	High

ROBIS tool to assess risk of bias in systematic reviews

Table S12. GRADE assessment of studied outcomes. (Until end-of original study [RCT])

Outcome	Number of Participants (Studies)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Quality	Best Estimate of TG Effect
ESRD or Dialysis	27 802 (5)	Moderate Limitations	Inconsistent	No serious Limitations	Imprecision	Not Detected	Low to Very-Low	RR 0.87 (0.71-1.06) (Hemmingsen et al.) ¹¹
Renal Death	15 760 (3)	Moderate Limitations	Consistent	No serious Limitations	Imprecision	Not Detected	Low to Moderate	RR 0.99 (0.55-1.79) (Coca et al.) ¹¹
Blindness	27 802 (5)	Moderate Limitations	Consistent	No serious Limitations	No serious Limitations	Not Detected	Moderate	RR 1.00 (0.96-1.05) (Boussageon et al.) ⁸
Clinical Neuropathy	27 049 (4)	Moderate Limitations	Consistent	No serious Limitations	No serious Limitations	Not Detected	Moderate	RR 0.99 (0.95-1.03) (Boussageon et al.) ⁸
All-Cause Mortality	27 802 (5)	Moderate Limitations	Inconsistent	No serious Limitations	No serious Limitations	Not Detected	Moderate	RR 1.00 (0.92-1.08) (Hemmingsen et al.) ¹¹
CV Mortality	27 802 (5)	Moderate Limitations	Inconsistent	No serious Limitations	No serious Limitations	Not Detected	Moderate	RR 1.06 (0.94-1.21) (Hemmingsen et al.) ¹¹
Non-Fatal MI	27 802 (5)	Moderate Limitations	Consistent	No serious Limitations	No serious Limitations	Not Detected	Moderate To High	RR 0.87 (0.77-0.98) (Hemmingsen et al.) ¹¹
Stroke	27 802 (5)	Moderate Limitations	Consistent	No serious Limitations	No serious Limitations	Not Detected	Moderate To High	RR 1.00 (0.84-1.19) (Hemmingsen et al.) ¹¹
Amputation or PVD	17 551 (4)	Moderate Limitations	Inconsistent	No serious Limitations	Imprecision	Not Detected	Moderate To High	RR 0.98 (0.84-1.13) (Boussageon et al.) ⁸ RR 0.65 (0.45-0.94) (Hemmingsen et al.) ¹¹
Severe Hypoglycemia	27 049 (4)	Moderate Limitations	Consistent	No serious Limitations	No serious Limitations	Not Detected	Moderate To High	RR 2.18 (1.53-3.11) (Hemmingsen et al.) ¹¹
*Microalbuminuria	27 802 (5)	Moderate Limitations	Consistent	Moderate to Serious Limitations	No serious Limitations	Not Detected	Moderate	RR 0.86 (0.76-0.96) ¹⁴ Coca et al.
*Photocoagulation	27 802 (5)	Moderate Limitations	Consistent	Moderate to Serious Limitations	No serious Limitations	Not Detected	Moderate	RR 0.77 (0.61-0.97) (Hemmingsen et al.) ¹¹

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